EPA Reviewer: Lisa Austin, Ph.D. **Signature:** [signature] **Date:** 7/30/09
Registration Action Branch 1, Health Effects Division (7509C)
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HED Executive Summary Cover for the attached OECD Formatted DATA EVALUATION RECORD

STUDY TYPE: Mechanistic-porphyrin analysis supplementary (rat); OECD 452.

PC CODE: 118203 **DP BARCODE:** D349929

TEST MATERIAL (PURITY): BAS 800 H (94.2%)

SYNONYMS: AC 433379; BASF Reg. No. 4054449, saflufenacil

CITATION: Cunha, G., Mellert, W., Deckardt, K. et al. (2006) BAS 800 H Supplementary mechanistic study in Wistar rats – total porphyrin analysis Administration in the diet over 8 weeks. Experimental Toxicology and Ecology, BASF Aktiengesellschaft 67056 Ludwigshafen, FGR. Report Number(s) 48C0414/01165. BASF Doc ID 2005/1026344. October 10, 2005. MRID 47128131. Unpublished.

SPONSOR: BASF Aktiengesellschaft, Ludwigshafen/Rhein, FRG.

EXECUTIVE SUMMARY:

In a repeat-dose mechanistic toxicity study (MRID 47128131), BAS 800 H (94.2%) was administered in the diet to groups of Wistar rats, 10/sex/group, at 0, 1, 5, or 25 ppm (♂ = 0, 0.1, 0.4, 2.0; ♀ = 0, 0.1, 0.5, 2.3 mg/kg bw/d, respectively) for an eight week period. The rats were examined for signs of toxicity and mortality twice a day. Body weights and food consumption were determined once a week. Blood and feces from all rats were sampled after 1, 2, 4, and 8 weeks of BAS 800 H treatment. Hematological examinations were performed and total porphyrin concentrations in feces were measured. At study termination, all rats were sacrificed under CO_2 anesthesia and assessed for gross pathological changes.

There were no adverse effects of treatment on mortality, clinical observation, body weight, food consumption or hematological parameters. Dietary administration of BAS 800 H at 25 ppm caused an increase in porphyrin in feces of male (237%) and female (61%) rats, while BAS 800 H at 5 ppm caused an increase (127%) in fecal porphyrin only in males. At 1 ppm, there were no effects on porphyrin excretion in the feces.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Flagging and Data Confidentiality statements were provided.

This Executive Summary was prepared for the United States Environmental Protection Agency, Office of Pesticide Program, Health Effects Division Use.

Much of the text was generated by the submitter(s) in OECD format. However, this document has undergone critical scientific analysis in comparison to the study report and modified as needed.

Reviewer #: Steve Wong, Ph.D., Date: August 28, 2008

APLICANT: BASF Corporation

STUDY TYPE: Mechanistic study – total porphyrin analysis in rat.

TEST MATERIAL (PURITY): BAS 800 H (94.2%)

SYNONYMS: AC 433379; BASF Reg. No. 4054449

CITATION: Cunha, G., Mellert, W., Deckardt, K. et al. (2006) BAS 800 H Supplementary mechanistic study in Wistar rats – total porphyrin analysis Administration in the diet over 8 weeks. Experimental Toxicology and Ecology, BASF Aktiengesellschaft 67056 Ludwigshafen, FGR. Report Number(s) 48C0414/01165. BASF Doc ID 2005/1026344. October 10, 2005. Unpublished. [PMRA # 1547099]

SPONSOR: BASF AG, Ludwigshafen/Rhein, FRG

EXECUTIVE SUMMARY:

In a repeat-dose mechanistic toxicity study, BAS 800 H (94.2%) was administered in the diet to groups of Wistar rats, 10/sex/group, at 0, 1, 5, or 25 ppm (♂ = 0, 0.1, 0.4, 2.0; ♀ = 0, 0.1, 0.5, 2.3 mg/kg bw/d, respectively) for an eight week period. The rats were examined for signs of toxicity and mortality twice a day. Body weights and food consumption were determined once a week. Blood and feces from all rats were sampled after 1, 2, 4, and 8 weeks of BAS 800 H treatment. Hematological examinations were performed and total porphyrin concentrations in feces were measured. At study termination, all rats were sacrificed under CO_2 anesthesia and assessed for gross pathological changes.

There were no adverse effects of treatment on mortality, clinical observation, body weight, food consumption or hematological parameters. Dietary administration of BAS 800 H at 25 ppm caused an increase in porphyrin in feces of male and female rats, while BAS 800 H at 5 ppm caused an increase in fecal porphyrin only in males. At 1 ppm, there were no effects on porphyrin excretion in the feces.

For porphyrin effects, the NOAELs were 1 and 5 ppm for male and female rats, respectively.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

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I. MATERIALS AND METHODS

A. MATERIALS:

1.

Test material:	BAS 800 H (N'-[2-chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)benzoyl]-N-isopropyl-N-methylsulfamide)
Description:	Solid crystalline / bright-beige; stored at room temperature
Lot/Batch #:	COD-000227
Purity:	94.2% a.i.
Compound stability:	The stability under the storage conditions was guaranteed by the Certificate of Analysis. The homogeneity of the test material was confirmed by analysis.
CAS #:	372137-35-4

2. **Vehicle and/or positive control:** The test substance was administered in the diet.

3. **Test animals:**

Species:	Rat	
Strain:	Wistar CrlGlxBrlHan:WI	
Age/weight at study initiation:	Age: ♂ = 42±1, ♀ = 43±1 days Mean weight: ♂ = 136. 9-167.3; ♀ = 112.7-141.3 g	
Source:	Charles River, Sulzfeld, Germany	
Housing:	Singly in DK III stainless steel wire mesh cages (floor area about 800 cm^2)	
Diet:	Kliba maintenance diet mouse/rat "GLP", meal, supplied by Provimi Kliba SA, Kaiseraugst, Switzerland; *ad libitum*	
Environmental conditions:	**Temperature:** **Humidity:** **Air changes:** **Photoperiod:**	20-24°C 30-70% no information ("*in fully air-conditioned room*") 12h dark / 12h light
Acclimation period:	At 7-8 days	

B. STUDY DESIGN:

1. **In life dates:** Start: September 7, 2004 End: August 25, 2005

2. **Animal assignment:**

Animals were assigned to test groups via a randomization protocol provided by a computer. The test groups are noted in Table 1.

Table 1: Study design

	♂				♀			
ppm	0	1	5	25	0	1	5	25
mg/kg bw/d	0	0.1	0.4	2.0	0	0.1	0.5	2.3
N	10	10	10	10	10	10	10	10

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3. **Diet preparation and analysis:**

For each concentration, BAS 800 H was weighed out and mixed with appropriate amounts of food, depending on dose group to obtain the desired concentrations. The BAS 800 H preparations were mixed in intervals of no longer than 7 weeks.

The stability of BAS 800 H in the diet over a period of 49 days was performed on a comparable batch. The stability of 1 ppm of BAS 800 H in the diet over 69 days at room temperature was verified in parallel to the study. Homogeneity analyses of BAS 800 H preparations were demonstrated in samples of the low concentration at the start of the study. These samples also served as concentration control analyses. Additional concentration control analyses were performed with samples drawn from the mid and high concentration at the start of the administration period.

Results:

Stability:
Based on the analysis of a 53.5 ppm sample, the analytical concentrations at days 9, 34, and 49 were 102.7, 95.3, and 97.9% of the nominal concentration. For a 1 ppm sample, the analytical concentration at day 69 was 109% of the nominal concentration. The analytical data verified the stability of BAS 800 H in the diet.

Homogeneity and concentration:
Concentration analysis of 1, 5, and 25 ppm samples showed analytical concentrations ranged from 95.0 to 108.0% of the nominal concentrations. Homogeneity analysis of 1 ppm samples showed analytical concentrations ranged from 95.0 to 108% of the nominal value.

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the study animals was acceptable.

4. **Statistics:**

Parameter	Statistical test	References
Food consumption, body weight, body weight change, food efficiency	A comparison of each group with the control group using the Dunnett-test (2-sided) for the hypothesis of equal means	Dunnett, C.W. (1955): A multiple comparison procedure for comparing several treatments with a control. JASA, Vol. 50, 1096-1121 Dunnett, C.W. (1964). New tables for multiple comparisons with a control. Biometrics, Vol. 20, 482-491
* Significantly different (p <0.05) from the control. ** Significantly different (p <0.01) from the control.		

C. **METHODS**

1. **Dosing:**

The test substance was administered daily in the diet for 8 weeks. Control rats received ground diet only.

2. **Observations:**

The rats were examined for overt signs of toxicity or mortality twice a day on weekdays and once a day on Saturdays, Sundays, and public holidays.

3. **Body weight:**

Body weight was determined before the start of the administration period in order to randomize the animals. The weights were then determined on day 0 and weekly thereafter.

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4. Food and water consumption and compound intake:

Individual food consumption was determined weekly and calculated as mean food consumption in g/rat/d. Food efficiency (group means) was calculated based on individual values for body weight and food consumption. The mean daily intake of test substance (group means) was calculated based upon individual values for body weight and food consumption. Water consumption was observed daily by visual inspection of the water bottles for any overt changes in volume.

5. Clinical pathology:

Blood was collected from the retro-orbital venous plexus of fasted animals under Isoflo® anesthesia. For feces sampling individual animals were transferred to metabolism cages (withdrawal of food and water) and the specimens were collected overnight and analyzed for total porphyrin using the spectrophotometrical method. The following hematological parameters were investigated.

x	hematocrit (Hct)	x	hemoglobin (Hb)	x	mean corpuscular Hb (MCH)
x	platelet count	x	reticulocyte count	x	mean corpuscular volume (MCV)*
x	erythrocyte count (RBC)			x	mean corpuscular Hb concentration (MCHC)*
x	erythrocyte morphology				

6. Sacrifice and pathology:

All surviving rats were sacrificed by CO_2 after a fasting period (withdrawal of food and water) for about 16 to 20 h and subjected to gross pathological examination.

II. RESULTS

A. Mortality and clinical signs of toxicity:

No animals died during the study period. There were no treatment-related findings.

B. Body weight and weight gain:

No changes in body weight and body-weight gain were observed in all treated rats.

C. Food and water consumption and compound intake:

1. Food and water consumption and food efficiency:

Food consumption was similar among test and control groups. Food efficiency was found slightly but statistically significantly increased in males at 25 ppm on study day 27. This single increase in food efficiency had no biological relevance and was likely to be incidental in nature. No overt changes in water intake were observed.

2. Compound consumption: See Table 1 for the mean daily test substance intake in mg/kg bw/d.

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D. Clinical pathology:

1. Hematology: There are no treatment-related changes in the hematological parameters measured.

2. Porphyrins and precursors: Table 2

Throughout the study statistically significant dose-dependent increases in porphyrin level were found in the feces of the males at 5 and 25 ppm. In the females, significantly higher porphyrin concentrations were noted in the feces of animals at 25 ppm on days 7, 14, and 28.

Table 2: Total porphyrin values (µmol/L) in feces, mean±SD

	♂ (N = 10/group)				♀ (N = 10/group)			
ppm	0	1	5	25	0	1	5	25
mg/kg bw/d	0	0.1	0.4	2.0	0	0.1	0.5	2.3
day 7	76.1±29.4	97.6±43.5	**109±40.4***	**283±60.5****	103±30.5	88.5±40.6	109±49.8	**175±60.9****
day 14	48.8±31.5	46.3±20.5	**75.9±36.9***	**207±74.0****	76.9±54.7	70.9±35.0	95.6±38.7	**128±44.1***
day 28	57.2±26.6	58.8±26.8	**116±56.8***	**204±70.7****	71.2±24.3	70.6±32.9	87.5±34.0	**145±39.6****
day 57	48.4±19.6	58.2±15.8	**110±61.1***	**163±57.0****	86.7±23.4	109±54.6	102±40.3	140±63.0

Data taken from Table IB. pages 88-103 of Report; * ≤0.05; ** ≤0.01; bold values are considered treatment-related

E. Sacrifice and pathology: There were no treatment0related gross pathological findings.

III. DISCUSSION

A. Authors' conclusions:

"Clinical pathology examination revealed no treatment-related changes in the red blood cell parameters of either sex at all time points. Total porphyrin measurements showed significantly higher total porphyrin levels in the feces of the males at 5 ppm and 25 ppm and in the females at 25 ppm. These findings are considered to be treatment-related and are a consequence of increased accumulation and excretion of porphyrins due to inhibition of protoporphyrinogen IX oxidase by the test compound.

In conclusion, the no observed effect level (NOEL) for altered porphyrin metabolism in Wistar rats after 8 weeks of BAS 800 H can be considered as being 1 ppm for males and 5 ppm for females."

B. Reviewer's comments:

The study is a non-guideline mechanistic study assessing porphyrin deposition and excretion in the feces of rats. The findings of this study are useful as supplementary data. The authors' conclusions are valid.